REMARKS

Amendments to the Specification

Applicants have amended the specification to correct some obvious errors.

For example, the specification as filed indicated on lines 13-16 of page 19 that certain ovalbumin antibodies could be combined, especially, with "anti-**native** ovalbumin monoclonal antibodies such as PDOA1 and PDOA2." However, PDOA1 and PDOA2 are indicated repeatedly in the specification as being anti-**denatured** ovalbumin monoclonal antibodies. See, *e.g.*, paragraph [0107] (page 63), in which PDOA1; FERM ABP-10275 and PDOA2; FERM ABP-10276 are indicated as being antibodies against denatured ovalbumin (RCMOA, or reduced carboxymethylated ovalbumin). The "N" in the nomenclature of monoclonal antibodies in the present application stands for "Native," and the "D" stands for "Denatured." Therefore, line 15 of page 19 has been amended to indicate "anti-**denatured** ovalbumin monoclonal antibodies such as PDOA1." Similar corrections have been made in the description of Figures 12 and 13 (paragraph [0019]) and in paragraphs [0026] and [0038].

Some obvious spelling or typographical errors have been corrected in paragraphs [0038], [0040], [0099], [0107] and [0131].

In Table 10 of paragraph [0109], the indication of "(native + denatured)" at the bottom of the table was inadvertently omitted from the specification as filed. Support for the re-addition of this terminology is found, *e.g.*, in the parent PCT application (PCT/JP2005/003799) from which this national stage application is derived.

The amendments do not add new matter and are fully supported by the specification.

Written description rejection of claims 105 and 112 (biological deposit)

Applicants disagree with the allegation by the Examiner that the biological samples (hybridomas) which were deposited in depositories that were described at the end of paragraph [0042], as amended in the Reply of September 16, 2009, and whose deposit papers were filed with that Reply, do not fulfill the terms of the Budapest Treaty. To further supplement the evidence that has already been presented, applicants attach to the present Reply a copy of the WIPO pages that describe the Japanese depositories as being in accordance with the Budapest Treaty. In addition, applicants note that the MPEP lists this depository (listed as: International

Patent Organism Depositary (IPOD); AIST Tsukuba Central 6; 1-1, Higashi 1-chome; Tsukuba-shi, Ibaraki-Ken 305-8566) as an acceptable depository in Japan.

Withdrawal of the rejection is requested.

Rejection of claims 103-105 and 112 under 35 USC 112, first paragraph (Written Description)

At the outset, applicants wish to clarify that the presently claimed method is a method for detecting an allergen (either a native ovalbumin, a denatured ovalbumin, or a combination of both forms of ovalbumin), by simultaneously using two pairs of monoclonal antibodies, one pair which recognizes native ovalbumin and the other pair which recognizes denatured ovalbumin. In each of the pairs of monoclonal antibodies, the two monoclonal antibodies recognize different epitopes of the ovalbumin (either native or denatured) that is being detected. In a food product, either native and denatured forms of an allergen (*e.g.*, ovalbumin), or a combination of the two forms, may be present. A method of the present invention allows for the detection of ovalbumin in a sample, regardless of whether the albumin is in a native or a denatured form. Claims 103 and 104 have been amended to clarify this aspect of the claimed method. These claims now recite "detecting native and denatured albumen allergen in the sample."

Claim 103 recites one embodiment of the method: a sandwich procedure. This method is illustrated in the attached diagram. It is noted that the positions of the epitopes etc. in the diagram are not precisely drawn. Rather, the diagram illustrates the general nature of the claimed invention, as is disclosed, *e.g.*, in paragraph [0015] of the specification. The diagram is provided merely for reference purposes. In the first step of the sandwich procedure, a sample suspected of containing an albumen allergen is reacted with an (one or more) insoluble (insolubilized) carrier to which has been bound a first MAb which recognizes native ovalbumin and a first MAb which recognizes a denatured form of ovalbumin. The immune complex formed in this first step is then reacted with a second set of MAbs, one of which recognizes native ovalbumin, but reacts with a different epitope of native ovalbumin than is recognized by the first MAb against native ovalbumin, and the second of which recognizes denatured ovalbumin, but reacts with a different epitope of denatured ovalbumin than is recognized by the first MAb against denatured ovalbumin. The second MAbs are labeled. The labeled immune complex formed in this second step is then detected.

In other words, claim 103 enables the detection of an ovalbumin, whether it is native or denatured, by simultaneously performing the following aspects of the method, (A) and (B):

(A)

(a) preparing an immune complex by allowing an albumen allergen in the sample to contact an insolubilized-carrier bound to a first **anti-albumin monoclonal antibody recognizing a native ovalbumin**;

(b) preparing a labeled immune complex by allowing the immune complex prepared in step (a) to contact a labeled second **anti-albumin monoclonal antibody recognizing a native ovalbumin,** wherein the second monoclonal antibody recognizing a native ovalbumin recognizes an epitope that is different from the one recognized by the first monoclonal antibody recognizing a native albumin; and

(c) detecting **a native albumen allergen** in the sample by detecting the labeled immune complex prepared in step (b) (*e.g.*, by using "anti-native ovalbumin monoclonal antibodies such as PNOA1 and PNOA2"); and

(B)

(a) preparing an immune complex by allowing an albumen allergen in the sample to contact an insolubilized-carrier bound to a first **anti-reduced carboxymethylated albumin monoclonal antibody recognizing a denatured ovalbumin**;

(b) preparing a labeled immune complex by allowing the immune complex prepared in step (a) to contact a second **anti-reduced carboxymethylated albumin monoclonal antibody recognizing a denatured ovalbumin**, wherein the second monoclonal antibody recognizing a denatured ovalbumin recognizes an epitope that is different from the one recognized by the first monoclonal antibody recognizing a denatured ovalbumin; and

(c) detecting **a denatured albumen allergen** in the sample by detecting the labeled immune complex prepared in step (b) (*e.g.*, by using "anti-denatured ovalbumin monoclonal antibodies such as PDOA1 and PDOA2").

The same principle applies to the immunoassay of amended claim 104, which recites an immunochromatography method. This immunoassay is also illustrated in the attached diagram.

Thus, contrary to the allegation in the Office Action, claims 103 and 104 do not recite individual assays in which two labeled antibodies are detected separately, rather than being detected simultaneously. Rather, the two different sets of antibodies are used and detected simultaneously in the assay. An assay of the invention allows for the detection of ovalbumin in a sample, with a high degree of accuracy, regardless of whether the albumin is in a native or a denatured form.

Support for the amendments to claims 103 and 104 indicating that the claimed methods can detect native and denatured ovalbumin in a sample can be found throughout the present specification, *e.g.* in the Examples and in paragraph [0026], which states that "by using the combination of anti-native ovalbumin monoclonal antibodies such as PNOA1 and PNOA2, and anti-denatured ovalbumin monoclonal antibodies such as PDOA1 and PDOA2, or especially by combining anti-native ovalbumin monoclonal antibodies such as PNOA1 and PNOA2 with anti-denatured [as corrected in the amendment to the specification filed with the present Reply] ovalbumin monoclonal antibodies such as PDOA1 and PDOA2, sandwich ELISA or immunochromatography can be performed more advantageously. For example, by using these antibodies, native ovalbumin and/or denatured ovalbumin in foods can be analyzed qualitatively and quantitatively even at a concentration between 1.0 to 10.0 ppb by sandwich ELISA."

Support for the amendment to claims 103 and 104 indicating that the monoclonal antibodies used in the methods are "a first anti-albumin monoclonal antibody recognizing a native ovalbumin **and** a first anti-reduced carboxymethylated monoclonal antibody recognizing a denatured ovalbumin" is supported, *e.g.*, in paragraph [0025] of the specification: "Methods for detecting albumen allergens of the present invention are not particularly limited as long as it is an immunological method for detecting albumen allergens using monoclonal antibodies recognizing native albumen allergens **and** monoclonal antibodies recognizing denatured albumen allergens simultaneously".

In view of the amendments to claims 103 and 104, Applicants believe that the Written Description rejection has been overcome, and request withdrawal of the rejection.

Rejection of claims 103-105 under 35 USC 112, second paragraph (indefiniteness)

Claims 103-105 and 112 have been amended to address the Examiner's concerns, rendering the rejection moot.

Withdrawal of the rejection is requested.

Rejection of claims 103 and 105 under 35 USC 103(a) over Narita *et al.*, in view of Kilshaw *et al.* and Mine *et al.*

Narita *et al.*

This reference is cited by the Examiner for its alleged disclosure of the use of monoclonal antibodies (MAbs) against native or heat-denatured ovomucoid in immunoassays to detect common food allergens. However, although Narita *et al.* may describe the use of MAbs that are specific for native or denatured ovomucoid, the reference does not suggest or disclose an assay which both forms of MAbs are used, together, in a single sandwich assay, to detect either a native or a denatured form of an albumen allergen.

Kilshaw *et al.*

The Examiner concedes that Narita *et al.* does not teach the use of antibodies against other albumen allergens, such as ovalbumin; and cites Kilshaw *et al.* for its alleged disclosure of MAbs made against native and denatured forms of ovalbumin. However, Kilshaw *et al.* does not correct the deficiency of Narita *et al.*, in that Kilshaw *et al.*, also, discloses that its monoclonal antibodies are used singly, rather than in combination, as is recited in the presently claimed methods. The sandwich assays described in Kilshaw *et al.* use a combination of a MAb with anti-ovalbumin rabbit serum as a secondary antibody, not the use of two monoclonal antibodies.

A review of figures presented in Kilshaw *et al.* shows that two monoclonal antibodies were never used in combination in any individual assay.

Fig. 1 describes sandwich and direct ELISA assays.

Fig. 1-a. NOA was coupled to an ELISA plate with rabbit antibodies (native ovalbumins). NOA-2 and NOA-5 reacted with the antigen, while DOA-1 and DOA-5 did not.

Fig. 1-b. It is shown that DOA-1 and DOA-5 reacted with DOA (denatured ovalbumin) directly adsorbed on an ELISA plate, but NOA-2 and NOA-5 did not. However, since the rabbit antibody is a polyclonal antibody, this assay is completely different from the sandwich ELISA

assay of the present invention, which is performed using a combination of two monoclonal antibodies.

Fig. 3 describes a direct ELISA assay (where the denaturation of OA on adsorption to an ELISA plate is assessed with monoclonal antibodies). The plate was coated with NOA or DOA in a range of concentrations, and it is reported that NOA-2 and NOA-5 showed a reduced reactivity to the immobilized NOA on the plate, and DOA-1 and DOA-5 both reacted with both of immobilized NOA and DOA on the plate.

The experiment was conducted by assaying samples individually, with either a monoclonal antibody against native OA or against denatured OA. As a result of this experiment, the authors caution against using a PVC plate in ELISA assay. The paper states that "An assay plate was coated with denatured or native OA in a range of concentrations and then tested with monoclonal antibodies to the two forms of the protein. Fig. 3 shows that monoclonal antibodies to denatured OA bound equally well to a coating of native or urea-denatured protein. In contrast, monoclonal antibodies to native OA gave negative results with the native molecule except at the very highest coating levels. The apparent conformation change on adsorption of OA to PVC was observed also in ELISA inhibition test using rabbit antiserum" (page 483, line 42 onwards).

Fig. 5 shows the result of an inhibition test on human sera, revealing that NOA was inhibited by NOA, while DOA, CNBr peptide, and Tryptic peptides did not work as an inhibitor (OA denaturation on adsorption on an ELISA plate was assessed by rabbit antibody). Again, none of the assays employed the use of a combination of two monoclonal antibodies.

Kilshaw *et al.* perform sandwich ELISA assays using anti-ovalbumin rabbit serum and monoclonal antibodies (*e.g.* in Figs, 1 (a) and 4 (c)), but they do not perform a sandwich ELISA assay using a combination of monoclonal antibodies in any of their tests. Thus, Kilshaw *et al.* fails to remedy the defects of Narita *et al.*, in that Kilshaw *et al.* also fails to describe an assay in which its monoclonal antibodies are used in combination, as is recited in the presently claimed methods.

Mine *et al.*

Mine *et al.* is cited in the Office Action for its alleged disclosure of similarities of polyclonal antibodies (not MAbs) which are prepared against reduced carboxymethylated denatured ovalbumin and heat denatured ovalbumin. It is not clear what the relevance is of this reference to the presently claimed invention, at least because the antibodies used in the studies of

Mine *et al.* are polyclonal antibodies in sera, rather than monoclonal antibodies. Like Narita *et al.* and Kilshaw *et al.*, Mine *et al.* also fails to suggest or disclose the use of two types of monoclonal antibodies, which recognize a native or a carboxymethylated denatured form of an albumen, in a single assay. Thus, Mine *et al.* fails to remedy to defects of Narita *et al.* or Kilshaw *et al.*, taken individually or together.

With regard to claim 105, none of the cited references, individually or taken together, teaches the particular monoclonal antibodies or hybridomas recited in that claim.

For at least the preceding reasons, applicants maintain that claims 103 and 105 are not rendered obvious by the cited references, and thus request that the rejection be withdrawn.

Rejection of claims 104 and 112 under 35 USC 103(a) over Narita *et al.*, Kilshaw *et al.* and Mine *et al.*, further in view of May *et al.* and Yueng *et al.*

Claims 104 and 112 depend from claim 103. As discussed above, the first three of the cited references, taken individually or together, do not render claim 103 obvious. Therefore, the disclosures in the two additional references of methods for conducting test strips do not remedy the defects of the first three references, and thus do not render claims 104 and 112 obvious. Withdrawal of the rejection is requested.

For at least the preceding reasons, applicants contend that the cited combination of references does not render obvious the presently claimed method for detecting albumen allergens. Applicants respectfully request that the rejection be withdrawn.

In view of the preceding amendments and arguments, it is believed that the application is in condition for allowance, which action is respectfully requested.

Should any additional fee be deemed due, please charge such fee to our Deposit Account No.22-0261, referencing docket number 31671-235624 and advise us accordingly.

Dated: **April 7, 2010**

Respectfully submitted,

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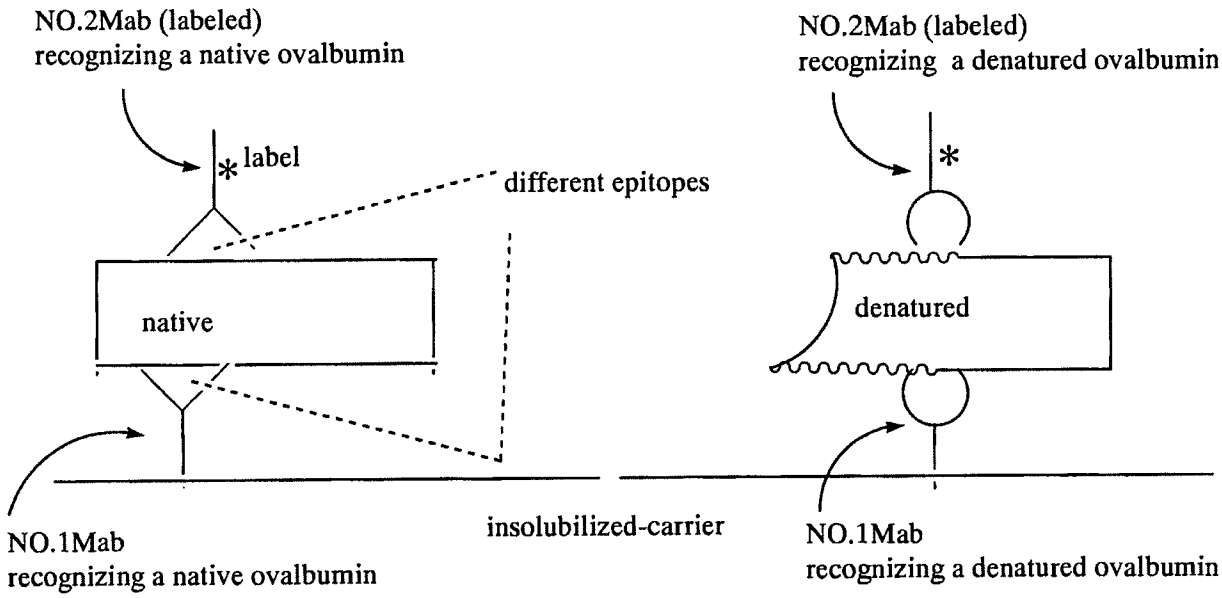
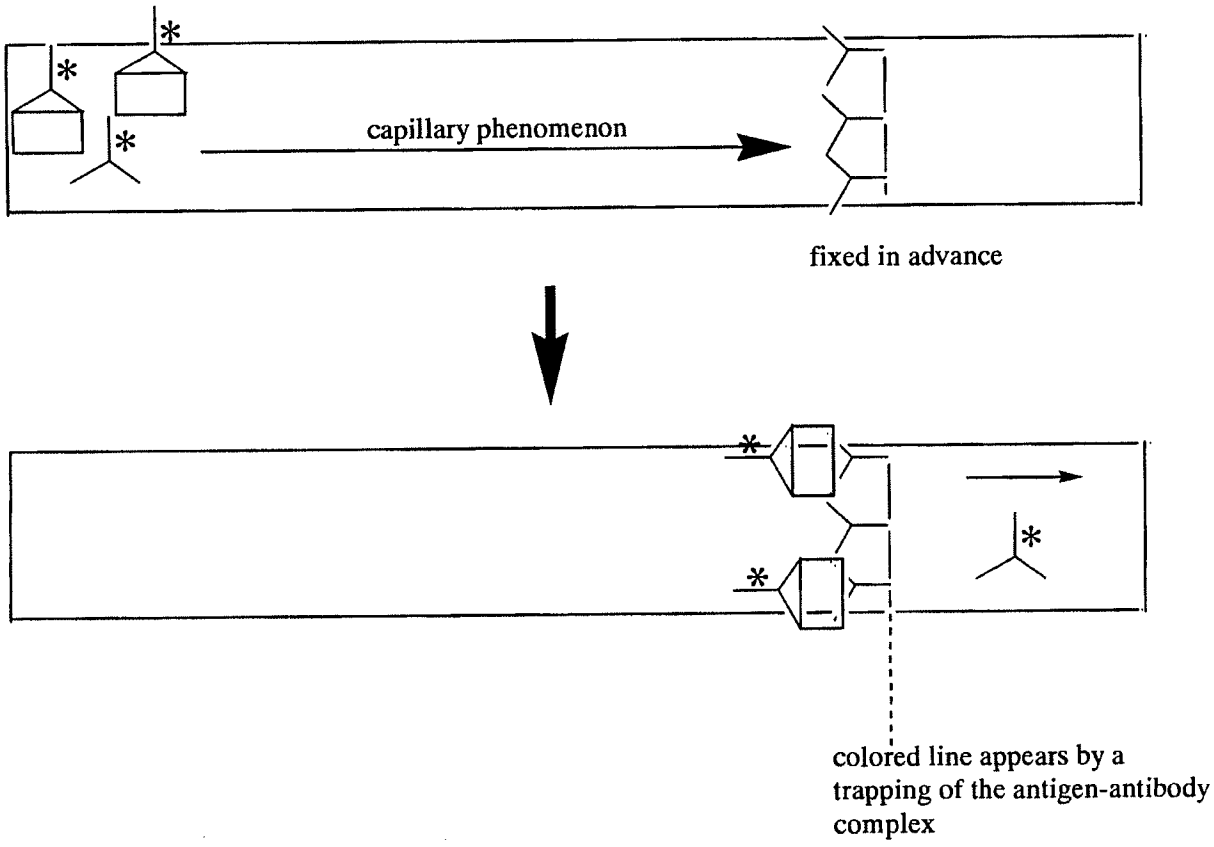
SANDWICH ELISA



Immunochromatography



Budapest Notification No. 252
Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure

Communication by the Government of Japan Regarding the Extension of the List of Kinds of Microorganisms accepted by, and a New Schedule of Fees Charged by, the National Institute of Technology and Evaluation, Patent Microorganisms Depositary (NPMD)

The Director General of the World Intellectual Property Organization (WIPO) presents his compliments to the Minister for Foreign Affairs and has the honor to notify him of the receipt from the Government of Japan, on December 22, 2006, of a written communication dated December 20, 2006 (ref. KN/WP/488), regarding the extension of the list of kinds of microorganisms accepted by, and a new schedule of fees charged by, the National Institute of Technology and Evaluation, Patent Microorganisms Depositary (NPMD), an international depositary authority under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, done at Budapest on April 28, 1977, as amended on September 26, 1980 (see Budapest Notification No. 215 of April 1, 2004). The text of that communication is attached.

According to Article 7.1(b) of the Budapest Treaty and Rule 3.3 of the Regulations under the Budapest Treaty, the extension of the list of kinds of microorganisms accepted shall take effect on February 1, 2007. According to Rule 12.2(a) of the Regulations under the Budapest Treaty, the fees set forth in the said communication shall take effect on February 1, 2007, with the exception of the handling charge referred to in I.(d) of the schedule of fees which, according to Rule 12.2(c) of the Regulations under the Budapest Treaty, shall take effect on February 9, 2007, that is, on the thirtieth day following the publication of the changes by the International Bureau.

January 10, 2007

Text of the Communication by the Government of Japan Regarding the Extension of the List of Kinds of Microorganisms accepted by, and a New Schedule of Fees Charged by, the National Institute of Technology and Evaluation, Patent Microorganisms Depositary (NPMD)

[Original: English]

COMMUNICATION

The Permanent Mission of Japan to the International Organizations in Geneva presents its compliments to the World Intellectual Property Organization (WIPO) and, in relation to the Budapest Treaty on the International Recognition of Microorganisms for the Purposes of Patent Procedure, has the honor to transmit attached herewith the communication from its home Government regarding the extension of the list of kinds of microorganisms accepted for the deposit by, and a new schedule of fees charged by, the NITE Patent Microorganisms Depositary (NPMD).

Pursuant to Rule 3.3 of the Regulations under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, the extension of the list of kinds of microorganisms accepted by the National Institute of Technology and Evaluation, Patent Microorganisms Depositary (NPMD) will be as follows: animal cell cultures and embryos.

Pursuant to Rule 12.2 of the said Regulations, a new schedule of fees charged by the National Institute of Technology and Evaluation, Patent Microorganisms Depositary (NPMD) will be as follows (see following annex)

ANNEX

JP - JAPAN
INTERNATIONAL DEPOSITARY AUTHORITY

National Institute of Technology and Evaluation
Patent Microorganisms Depositary (NPMD)
2-5-8 Kazusakamatari
Kisarazu-city
Chiba 292-0818

Telephone: (81) 438 20 55 80
Facsimile: (81) 438 20 55 81
E-mail: npmd@nite.go.jp
Internet: http://www.nbrc.nite.go.jp/npmd/

KINDS OF MICROORGANISMS THAT MAY BE DEPOSITED

Actinomycetes, animal cell cultures, archea, bacteria, bacteriophages, embryos, fungi, plasmids (in hosts or not in hosts) and yeasts, EXCEPT:

- microorganisms which belong to biosafety level 3 or level 4 according to the NITE (National Institute of Technology and Evaluation) Classification.

- microorganisms which call for containment measures level P3 or P4 as described in the Ministerial Ordinance stipulating Containment Measures to be Taken in Type 2 Use of Living Modified Organisms for Research and Development (2004), which is based on the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (2003).

SCHEDULE OF FEES

		JPY
I.	Actinomycetes, archea, bacteria, bacteriophages, fungi, plasmids (in hosts or not in hosts) and yeasts:	
(a)	Storage (for 30 years)	
	- original deposit	139,000
	- new deposit	9,000
(b)	Issuance of communication under Rule 7.6	2,000
(c)	Issuance of viability statement	
	(i) if the viability test is to be carried out	16, 000
	(ii) based on the last viability test	2,000
(d)	Furnishing of a sample (plus handling charge) [1]	6,000
(e)	Issuance of attestation under Rule 8.2	2,000
II.	Animal cell cultures and embryos:	
(a)	Storage (for 30 years)	
	- original deposit	149,000
	- new deposit	10,000
(b)	Issuance of communication under Rule 7.6	2,000
(c)	Issuance of viability statement	
	(i) if the viability test is to be carried out	28,000

(ii)	based on the last viability test	2,000
(d)	Furnishing of a sample (plus handling charge) [2]	7,000
(e)	Issuance of attestation under Rule 8.2	2,000

Japanese consumption tax will be charged for (a) and (c)(i):
1. Plus 6,000 yen for handling to the foreign institution
2. Plus 35,000 yen for handling and delivery to the foreign institute